In support of this fact Applicant submits two expert declarations from Dr. Robert Samuel Langer from MIT who is considered an expert with respect to pharmaceutics, controlled release technology and delivery systems for drugs. His credentials are extensive and he is more than qualified to provide evidence as a basis to rebut the Examiner's obviousness rejection in that he clearly sets out the differences between the present claim set and the prior art. The Examiner is referred to his Declarations in this regard. Both declarations and the contents thereof are hereby incorporated in their entirety by reference.

Referring now to Duclos, United States Patent No. 5,776,495, the disclosure includes an extensive list of actives which are difficult, if not impossible to dissolve in water. The list is extensive and includes over 70 actives. Respectfully, it is submitted that there is no way that Duclos intended or at least perfected an understanding of how the various actives might be incorporated in a co-precipitate formulation. Frequently, within the pharmaceutical industry what might work in a technique with one active will not work with another. This is clearly supported in the declarations of Dr. Langer. No where within the Duclos reference is there any discussion of cefuroxime axetil other then a listing of cefuroxime (not the ester form thereof) in the list of actives. It appears that Duclos went to a particular reference manual and attempted to list all of the actives that were hardly soluable in water without substantiating that his invention would apply to that list of actives. Broad claims were not therefore allowed by the United States Patent Office as there is no enabling disclosure in Duclos that would enable one skilled in the art to determine and select cefuroxime from the entire list of 70 plus actives. What would motivate one skilled in the art to focus in on cefuroxime when there is no detailed discussion in Duclos of the advantages to be achieved in providing a co-precipitate as in Applicant's case. The Examiner has alleged that one skilled in the art would be motivated to do so; but Dr. Langer disagrees. Respectfully, the Examiner is not a person skilled in the art.

Referring now to Crisp, United States Patent No. 4,820,833, it is clear from the teachings of Crisp at column 2, line 15 that Crisp had surprisingly found that cefuroxime axetil is advantageously used in a highly pure substantially amorphous form. This teaching in Crisp is repeated through the disclosure and repeated again for example, at column 6 at line 9. It is clear therefore from the teachings of Crisp and the examples therein that it was intended by Crisp that the desired result would be highly pure substantially amorphous cefuroxime axetil. Applicant does not desire to provide a highly pure substantially amorphous form. In fact, by preparing a co-precipitate the opposite is true. Please refer to Dr. Langer's declarations in this regard. The teachings of Crisp therefore, point clearly away from the teachings of Duclos, and it is respectfully submitted that Duclos and Crisp would not be readily combined as they are somewhat mutually exclusive as covered by the case law previously provided to the Examiner. The Examiner is therefore referred back to that case law which is incorporated by reference. Utilizing Applicant's teaching as a blueprint, and finding the components in the prior art is not permitted.

Further there is no motivation to one skilled in the art in the teachings of Duclos to even review Crisp. How would one skilled in the art be motivated to pursue the teachings of Crisp if in fact, Crisp does not suggest combining the art and clearly to the contrary desires a highly pure substantially amorphous form of cefuroxime axetil. Duclos does not point directly to cefuroxime but only provides it in a general listing which is not enabling.

To the contrary, Applicant provides a disclosure and support for the following claims.

1. An enhanced bioavailable composition comprising a co-precipitate of cefuroxime axetil and a water-soluble excipient made by dissolving pure crystalline

cefuroxime axetil and the excipient in a suitable solvent, and recovering the co-precipitate, said composition having a disintegration time of at least 10 to 30 minutes and having a dissolution as determined by U.S. Pharmacopoeia 23rd Edition, of about 65% to about 80% in 20 minutes and about 80% to over 90% in 60 minutes.

15. An enhanced bioavailable composition comprising a co-precipitate of cefuroxime axetil and sorbital made by dissolving pure crystalline cefuroxime axetil and the sorbital in a suitable solvent, and recovering the co-precipitate, said composition having a disintegration time of at least 10 to 30 minutes and having a dissolution as determined by U.S. Pharmacopoeia 23rd Edition, of about 65% to about 80% in 20 minutes and about 80% to over 90% in 60 minutes.

According to Graham and John Deere, the scope and the content of the prior art has been determined and the differences between the claimed invention and the prior art have been set out. Further, a discussion of motivation not to be found in any of the prior art references consistent with Re: Sernacker reasoning has been put forward; both in this submission and in the declarations of Dr. Langer. There is nothing to suggest within Duclos to in fact select cefuroxime axetil as the active when preparing a co-precipitate. There is nothing within Crisp that would teach or motivate one skilled in the art to combine the teachings of Crisp with Duclos in that Crisp points in substantially the other direction, as discussed by Dr. Langer. In support of this position Applicant provides expert evidence from Dr. Langer as discussed above.

Dr. Langer's conclusions in his first affidavit are highlighted below as follows:

Para 11. "Thus, in my opinion, among the key novel and advantageous features of the formulations containing cefuroxime axetil with enhanced bioavailability claimed in the '598 patent application are (i) formulations which

do not require the presence of cefuroxime axetil in a highly pure, substantially amorphous form and (ii) formulations which do not require immediate disintegration or dissolution. With respect to the latter, in my opinion this is an important result when considering the absorptive properties of cefuroxime axetil in the gastrointestinal tract. As discussed in the article entitled "Nonlinear Intestinal Absorption of Cefuroxime Axetil in Rats" authored by Ruiz-Balaguer et al. that I was provided with as part of the file history of the '598 patent application, the authors demonstrated that cefuroxime axetil likely undergoes active absorption in the gastrointestinal tract via a process that is saturable. For example, it is stated on page 445 of this article that (column 1, paragraph 2):

> *"The absolute bioavailability of all newer oral ester prodrug cephalosporins is below 50 to 60% (15), which suggests an absorption mechanism through the mucosa with limited capacity."*

Similarly, it is stated on page 448 of this article that (column 1, paragraph 3):

> *"Results obtained here tend to indicate that an active transport mechanism could be involved in cefuroxime axetil absorption."*

Para 12. In my opinion, this is an important point to consider in relation to the formulations claimed in the '598 patent application. As described above, the state of the art as represented by the '833 and '270 patents taught that the following were requirements of oral dosage forms containing cefuroxime axetil with good bioavailability: (i) the presence of cefuroxime in a highly pure, substantially amorphous form (optionally admixed with various excipients) and (ii) immediate disintegration with subsequent rapid dissolution of cefuroxime axetil. However, immediate dissolution in the gastrointestinal tract may not be desired or optimal for drugs which are absorbed via an active, saturable

transport mechanism such as cefuroxime axetil. For such cases, immediate dissolution would result in locally high drug concentrations. **These locally high drug concentrations could result in a saturation of the transport mechanism, which could lead to reduced bioavailability of cefuroxime axetil due to hydrolysis prior to absorption.** (emphasis added) For example, it is stated on page 448 of the article authored by Ruiz-Balaguer et al. that (column 1, paragraph 6):

> *"In view of these observations, an important hydrolysis is in action, and that is one of the reasons for the poor bioavailability of cefuroxime axetil. On the other hand, the variability in the bioavailability obtained can be justified, in our opinion, by the existence of interindividual variability in the enzymatic activity of the intestinal esterase responsible for the hydrolysis of the prodrug, as the greater the hydrolized fraction is, the less the absorbable fraction would be."*

The formulations claimed in the '598 patent application can potentially circumvent this limitation on the bioavailability of cefuroxime axetil by slowing and spreading out over time the dissolution of cefuroxime axetil, which would reduce local concentrations of the drug and potentially avoid saturation of the transport mechanisms. (emphasis added) Additionally, slowing down the dissolution of cefuroxime axetil as taught in the '598 patent application can potentially provide the added advantage of eliminating the potential for either recrystallization or gelation of cefuroxime axetil due to locally high concentrations in the gastrointestinal tract. Thus, in my opinion and as I will discuss further below, a key novelty of the formulations disclosed in the '598 patent application is the identification of specific combinations of cefuroxime axetil and excipients such as sorbitol for the production of coprecipitated solid dispersions that possess optimized properties with respect to their dissolution and drug release behavior."

Para 15. "The inventors of the '495 patent clearly state that results seen for drug-containing formulations based on solid dispersions are very dependent on both the drugs and the excipients comprising the dispersions and **that results seen for one drug may be very different from results seen for other drugs. (emphasis added)** For example, it is stated in the '495 patent that (column 1, line 45 through column 2, line 4):

"It is also known that, for active substance absorption, the gastro-intestinal tract level of which is limited due to their low solubility in biological liquids, one of the possibilities offered to the galenist for the improvement of kinetics of dissolution is the production of solid dispersions. These solid dispersions (defined by Chiou et al. in J. Pharm. Sci. Vol. 60. Pp. 1281-1302. 1971) constitute systems which, depending on the process used for their production, may present different structures (see Ford. Pharm. Acta. Helv., Vol. 61, 3, pp 69-88, (1986) Bloch et al. Pharm. Acta. Helv., Vol. 62, pp 23-27, (1987)), corresponding to different crystallographic states. The vitreous state, though it is a solid state, draws near to a liquid state for its structural disorder. It is a little orderly state, easy to break and which improves substantially the rate of dissolution for less soluble components. ***Nevertheless, despite the great number of publications relating to the production of solid dispersions, especially for Macrogols or Poloxamers, this technique has not known any important development because of its lack of generality. In some cases, the rate of dissolution is great. In other cases, the rate of dissolution is weaker and makes one's way toward an asymptotic value. For the same drug and for the same concentration, it has been established very significant variations in rates of solubility in terms of the nature of co-fusing agent and even in certain cases, the impossibility to obtain a***

complete solubilization of the active component, even after a protracted time of contact." (Emphasis added.)

Para 39-42 "Thus, I disagree with the comments made by the U.S. Examiner in relation to this point. For example, in the Office Action Summary from the USPTO mailed on May 31 2002, the U.S. Examiner states that (page 5, paragraph 2):

"Applicant also argues that Crisp is different from the instant claims because Crisp requires cefuroxime axetil in highly pure substantially amorphous form. Applicant argues that this is mutually exclusive from the instant claims, as well as the teachings of Duclos, which both require a co-precipitate. The examiner respectfully disagrees. Stedman's Medical Dictionary (attached) defines amorphous as not crystallized. The same dictionary (also attached) defines precipitate as a solid separated out from a solution or suspension. These two terms are not mutually exclusive, as claimed by applicant. No where in the Crisp reference does it prohibit precipitation. Instead the Crisp reference simply prohibits any crystalline material from being present."

In my opinion, the U.S. Examiner misinterpreted the Applicant's argument described above concerning the claimed compositions of the '833 patent as being mutually exclusive from those of the '495 patent and the '598 patent application. It appears that the U.S. Examiner concluded that the claimed compositions of the '833 patent are not mutually exclusive from those of the '495 patent and the '598 patent application due to the fact that all of the compositions are likely substantially amorphous in nature. In contrast, it is my opinion that co-precipitation with an excipient as described in the '495 patent and the '598 patent application is mutually exclusive from the production of a highly pure phase of a drug as described in the '833 patent. For example, the production of a highly

pure phase of a material teaches the removal of any non-drug materials, whereas co-precipitation teaches the addition of non-drug materials (thus reducing the purity of the resultant drug-containing phase). (Emphasis added)

The Combined Teachings of the '833 and '495 Patents

Para 40. It is also my opinion that the combined teachings of the '833 and '495 patents do not make obvious the compositions disclosed in the '598 patent application. As I described above, it is my opinion that the '833 patent and the '495 patent teach in fundamentally different directions. (Emphasis added) The '833 patent focuses on the production of highly pure forms of amorphous cefuroxime axetil. In contrast, the '495 patent teaches the production of combinations of coprecipitated drugs and excipients in solid dispersion form, with no constraints provided as to whether the solid dispersions are crystalline in nature (i.e., eutectic systems), amorphous or some combination thereof.

Para 41. Thus, I disagree with the comments made by the U.S. Examiner with respect to this point. For example, in the Office Action Summary from the USPTO mailed on May 31 2002, the U.S. Examiner states that (page 4, paragraph 1):

> *"One of ordinary skill in the art would look to the broad teachings of Duclos et al., and apply the specific teachings of Crisp et al., such as the use of the specific form of cefuroxime axetil, as well as the use of spray-drying to evaporate off the solvent and cause formation of the precipitate (or co-precipitate)."*

Similarly, the Examiner states on page 4 that (paragraph 2):

> *"It is the position of the examiner that Duclos et al. disclose applicant's generic inventive concept, which is forming a co-precipitate from a therapeutic agent (such as cefuroxime) and a water soluble excipient. It is further the position of the examiner that a skilled practitioner would look to the appropriate art, such as Crisp et al., to discover more specifics concerning the specific active, cefuroxime. One of ordinary skill in the art would certainly be motivated to combine the teachings of these two references, in order to form a successful co-precipitate of cefuroxime and a hydrophilic excipient."*

I disagree with these statements. With respect to the broadness of the teachings of the '495 patent (Duclos et al.), as described above, specific information is only provided for compositions containing progesterone and estradiol, with the inventors of the '495 patent indicating that results seen for one drug and excipient combination cannot be assumed to be predictive for others (as evidenced by the quote from the '495 patent shown in paragraph 15 above). Thus, the '495 patent provides little to no information of use to a skilled formulator attempting to formulate a coprecipitate containing cefuroxime axetil and a water soluble, non-polymeric excipient such as sorbitol for example. (Emphasis added)

Para 42. Additionally, I do not believe that a skilled formulator would be motivated to combine the teachings of these two patents since, in my opinion, they teach in fundamentally different directions. The U.S. Examiner has asserted in the statements shown above that one skilled in the art would look to Crisp for the details related to forming a coprecipitate containing cefuroxime axetil in addition to an excipient. In my opinion, a skilled formulator attempting to follow the teachings of the '495 patent would not look to the '833 patent since the

'833 patent is based on and requires a highly pure, substantially amorphous product in order to facilitate the bioavailability of cefuroxime axetil. Again, as I described above, the '833 patent teaches towards obtaining a purified amorphous sample consisting essentially of only cefuroxime axetil. In contrast, the nature of forming a coprecipitate of a drug and an excipient teaches towards intimately combining significant amounts of a foreign material with said drug and thus significantly decreasing its purity."

Para 44. "In summary, it is my opinion that the teachings of the '495 and '833 patents, considered alone or in any combination, do not render obvious the claims in question of the '598 patent application, namely, novel coprecipitate compositions containing cefuroxetime axetil that possess optimized properties with respect to their dissolution behavior." (Emphasis added)

Dr. Langer's further conclusions in his second affidavit are also highlighted below as follows:

Para 13 "As is clearly evident in the table above and described in Exhibit B, a single glass transition temperature was detected for each of the amorphous samples made based on the teachings of the '598 patent application (Apotex 1 and 2), with each transition temperature being significantly lower than the glass transition temperature detected for the amorphous sample made based on the teachings of the '833 patent (GSK). **In my opinion, this clearly indicates that the Apotex 1 and 2 samples consist of a molecular level dispersion of cefuroxime axetil and excipient(s) (sorbitol for Apotex 1 and sorbitol and zinc chloride for Apotex 2), with the excipient(s) acting in effect as plasticizers (as I described above, sorbitol is known in some cases to act as a plasticizer in amorphous phases, with plasticizers being defined as materials that lower the glass transition of a given amorphous material). Thus, in my opinion,**

amorphous materials such as Apotex 1 and 2 described above are clearly not highly pure, substantially amorphous forms of cefuroxime axetil. (Emphasis added)

Para 14. Thus, in my opinion, these results confirm the fact that amorphous coprecipitates of cefuroxime axetil and excipients such as sorbitol and zinc chloride produced via spray-drying as described in the '598 and '676 patent applications are distinct and different from the highly pure, substantially amorphous forms of cefuroxime axetil produced via spray-drying as described in the '833 patent."

The Examiner is requested to carefully study these two Declarations from Dr. Langer and to consider them as a substantial part of this reply and thereafter reconsider and withdraw her rejections.

Applicant encloses herewith the Declarations of Dr. Langer under 37 C.F.R. 1.132 to provide evidence with regard to comparative tests results illustrated in the unexpected properties and superior results of Applicant's invention in relation to the prior art Crisp and Duclos. Applicant also provides the Declarations with the intention of interpreting the meaning of each reference for setting out the differences between the invention and the prior art by an expert. The Affidavits of Dr. Langer set forth both the facts and a detailed analysis of the facts in the case and does not merely set forth conclusions. His Affidavits are therefore very pertinent to the rejections that Applicant is rebutting. Please refer to In re May, 197 USPQ 601 (CCPA 1978) "*Appealed claims, of applicants who submitted rebuttal evidence in response to prima facie case of obviousness, must be considered in light of all evidence, and resulting obviousness determination must be made in such light.*" wherein it discusses that expert opinion may be provided which is relevant to the issues at hand and

said evidence must be considered by the Examiner and that the Applicant should expect closer scrutiny of the Declaration than those of the patent practitioner.

Applicant has therefore provided amendments and extensive expert evidence in submission to rebut the examiner's position , and full reconsideration is therefore respectfully requested.

Applicant has now amended the claims to limit the subject matter to the delayed disintegration of the composition which have an enhanced bioavailability to that which disintegrates within the range of 10 to 30 minutes and a dissolution as determined by U.S. Pharmacopoeia 23rd Edition, of about 65% to about 80% in 20 minutes and about 80% to over 90% in 60 minutes to allow for time for transport of the active toward the small intestine for dissolution and absorption. Please refer to Dr. Langer's first Declaration in this regard. This lack in the prior art is supported by the previously attached literature *Antimicrobial Agents and Chemotherapy, Feb. 1997, p. 445-448,* Nonlinear Intestinal Absorption Kinetics of Cefuroxime Axetil in Rats, *Ruiz-Balaguer et al.* in support of these statements and the claim amendments.

Should the Examiner require further data as evidence in support of this point, she is respectfully requested to advise Applicant's Agent, who would be more than happy to provide such data. It is therefore respectfully requested that the prior art be withdrawn and the claims in their amended forms be allowed.

Attached hereto as Exhibit A is a marked-up version of the changes made to the claims by the present amendment. The attached pages are entitled **"EXHIBIT A – CLAIMS WITH MARKINGS TO SHOW CHANGES".**

Also attached hereto as Exhibit B are three sheets that contain a clean set of all pending claims following entry of this amendment. These sheets are entitled **"EXHIBIT B – CLEAN SET OF ALL PENDING CLAIMS FOLLOWING ENTRY OF THE PRESENT AMENDMENT"**. All of the currently pending claims are consolidated in this list for the convenience of the Examiner.

Should the Examiner have any questions she is respectfully requested to contact Applicants' Agent, Neil H. Hughes at (905) 771-6414 at her convenience.

Respectfully submitted,

Neil H. Hughes, P.Eng.
Registration No. 33,636
Agent for the Applicant

NHH:mse
Enclosures

EXHIBIT A
CLAIMS WITH MARKINGS TO SHOW CHANGES

Please amend the following claims.

1. (Thrice Amended) An enhanced bioavailable composition comprising a co-precipitate of cefuroxime axetil and a water-soluble excipient made by dissolving pure crystalline cefuroxime axetil and the excipient in a suitable solvent, and recovering the co-precipitate, said composition having a disintegration time of at least 10 to 30 minutes and having a dissolution as determined by U.S. Pharmacopoeia 23rd Edition, of about 65% to about 80% in 20 minutes and about 80% to over 90% in 60 minutes.

15. (Thrice Amended) An enhanced bioavailable composition comprising a co-precipitate of cefuroxime axetil and sorbital made by dissolving pure crystalline cefuroxime axetil and the sorbital in a suitable solvent, and recovering the co-precipitate, said composition having a disintegration time of at least 10 to 30 minutes and having a dissolution as determined by U.S. Pharmacopoeia 23rd Edition, of about 65% to about 80% in 20 minutes and about 80% to over 90% in 60 minutes.

EXHIBIT B
CLEAN SET OF ALL PENDING CLAIMS FOLLOWING ENTRY OF THE PRESENT AMENDMENT

1. An enhanced bioavailable composition comprising a co-precipitate of cefuroxime axetil and a water-soluble excipient made by dissolving pure crystalline cefuroxime axetil and the excipient in a suitable solvent, and recovering the co-precipitate, said composition having a disintegration time of at least 10 to 30 minutes and having a dissolution as determined by U.S. Pharmacopoeia 23rd Edition, of about 65% to about 80% in 20 minutes and about 80% to over 90% in 60 minutes.

2. The composition of claim 1 comprising from about 40% to about 98% by weight cefuroxime axetil and from about 2% to about 60% by weight water-soluble excipient.

3. The composition of claim 1 comprising from about 75% to about 95% by weight cefuroxime axetil and from about 5% to about 25% by weight water-soluble excipient.

4. The composition of claim 1 comprising about 90% by weight cefuroxime axetil and about 10% by weight water-soluble excipient.

5. The composition of claim 1 wherein the water-soluble excipient is selected from the group consisting of povidone, hydroxy propyl cellulose, methycellulose, lactose, mannitol and sorbitol.

6. A process of production of the composition of claim 1 which comprises:

- dissolving the cefuroxime axetil and water-soluble excipient in a solvent or a mixture of solvents; and
- evaporating the solvent or solvents.

7. The process of claim 6 wherein acetone is used as solvent.

8. The process of claim 6 wherein the solvent or solvents are evaporated by spray-drying.

9. A pharmaceutical tablet comprising the composition according to claim 1.

10. The pharmaceutical tablet of claim 9 further comprising a disintegrant.

11. The pharmaceutical tablet of claim 10 wherein the disintegrant is a water-insoluble cross-linked polymer.

12. The pharmaceutical tablet of claim 10 wherein the disintegrant is selected from the group consisting of croscarmellose sodium, sodium starch glycolate and crospovidone.

13. The pharmaceutical tablet of claim 10 further comprising a lubricant.

14. The pharmaceutical tablet of claim 13 wherein the lubricant is stearic acid or a metallic stearate.

15. An enhanced bioavailable composition comprising a co-precipitate of cefuroxime axetil and sorbital made by dissolving pure crystalline cefuroxime axetil and the sorbital in a suitable solvent, and recovering the co-precipitate, said

composition having a disintegration time of at least 10 to 30 minutes and having a dissolution as determined by U.S. Pharmacopoeia 23rd Edition, of about 65% to about 80% in 20 minutes and about 80% to over 90% in 60 minutes.

16. The composition of claim 15 comprising about 90% cefuroxime axetil and about 10% sorbital.

17. A process of production of the composition of claim 15 which comprises:

- dissolving the cefuroxime axetil and sorbital in a solvent or a mixture of solvents; and
- evaporating the solvent or solvents.

18. The process of claim 16 wherein acetone is used as solvent.

19. A pharmaceutical tablet comprising the composition according to claim 15.

20. The pharmaceutical tablet of claim 19 further comprising a disintegrant selected from the group consisting of croscarmellose sodium, sodium starch glycolate and crospovidone.